associated with changed joint tissue whether or not measurable by presently available techniques." Is that a cyclic argument that you're presenting to us? Because if you can't measure the disease, you're saying it's still a disease state. And could you clarify that for me?

DR. SIMON: Sure, but remember that I predicated the whole idea on that it has to be characterized by symptoms. So, therefore, anybody that presents with symptoms, whether they measure change by any modality, have the disease. If they fulfill the characteristic clinical presentation and in this context, if they have no X-ray or other changes, it might be a diagnosis of exclusion that you've ruled out other forms of arthritides. And for those that don't know, there are about 100 other forms of arthritis besides osteoarthritis. And the diagnostician has to then utilize the best characteristics of taking a history and performing a physical exam.

That's the nature of the circular argument because, without having biochemical or biologic

markers that are diagnostic of the disease, we're only dependent upon our clinical acumen. Ostler would be happy.

DR. MILLER: Dr. Harris?

DR. HARRIS: Yes, one very quick question--actually, two very quick questions. One is there's no evidence, I assume, that this disease is familial? And the other question I wanted to ask you was: Have there been any studies that have looked at an array of factors, such as DNA micro arrays or proteomics, in evaluating any changes?

DR. SIMON: Well, the second question is the easiest one to answer. In fact, that's what's going on now. Dr. Abramson already alluded to the fact that his laboratory has actually changed its focus into looking at those particular areas, about looking at array analysis. So that's one.

Two, there is clearly a familial behavior associated with this process. It's particularly evidenced by my allusion to hereditary osteoarthrosis, which are the Heberdens and Bouchard's nodes that are clearly seen in families

and you can actually do demographics associated with that.

I would suggest that many would argue that much of the disease is familially defined, and I suspect we just don't know the extent of how familial it may actually be.

DR. MILLER: Dr. Felson?

DR. FELSON: No critical comment afterward. I thought it was a lovely communication of complexity--

DR. SIMON: Thank God.

DR. FELSON: The remarkable complexity of this. And I think the committee also needs to get a sense that we're not so confused, that we don't have operational definitions of these things. We do. And I think that's perhaps one of the things we need to talk about briefly because so much of the questioning has been doesn't everybody have a little of this, how do you define this disease. And I think Dr. Simon repeatedly made a very important point, and the ACR definition of it, which Dr. Altman chaired the committee for, and a

variety of other epidemiologic definitions of it, including the definition that the Osteoarthritis Initiative at the NIH is using, require one--are fairly consistent. They require frequent pain in the joint, plus radiographic evidence of disease in that joint, almost always defined as a definite osteophyte. Okay? And that's the threshold above which we characterize somebody as having osteoarthritis. You'll notice that requires a combination of symptoms and radiographic findings.

The mild stuff is harder because there's a lot of people, and perhaps even some in this room, given the frequency of this disease, who maybe don't have pain every day or don't have pain on most days, but have it whenever they go up and down stairs, which they might not do every day, or when they play tennis or something like that. And they don't, therefore, meet the rigorous criteria we've just laid out if they don't play tennis every day or several times a week. Those people we might call having mild disease or, you know, something like that, given the fact that they're not plagued

by symptoms all the time.

But I think we do have definitions, I guess. You can see that they're an attempt to draw a dichotomous line, a line in the sand, on what we all recognize to be a fairly continuous process. That there--and both elements, both the symptoms and the structural abnormalities are continuous here. There's a little tiny osteophyte in probably all of your joints somewhere, okay? And yet the serious structural disease is present only in a few of you. There may be occasional symptoms--I can tell you I have occasional knee symptoms--in many of you, but not to the point where we would say it's beyond that line we've drawn in the sand, that is, on most days of the past month, for example.

DR. SIMON: But, David, we draw that line in the sand to allow us to homogenize our patient populations for clinical studies. You would have to admit that we don't as often draw the line in the sand when we make a clinical ascertainment whether someone actually has a diagnosis of disease. And that's the dilemma that we have

because often our clinical trials, particularly epidemiologic, are not necessarily extrapolatable to the mild case without X-ray evidence, but they have to be studied somehow, and you want to enrich your inception cohort with the possibility of change so that you can see it within the window of opportunity of a clinical trial. That's the challenge to know whether clinical trials are truly naturalistic and, thus, really inform you about this incredibly heterogeneous process.

DR. MILLER: Thank you.

Our next speaker is Dr. James Witter, of the Center for Drug Evaluation and Research at FDA, to talk on the role of animal and *in vitro* models in osteoarthritis risk reduction.

DR. WITTER: Good afternoon. I've known Lee Simon for at least 20 years, and now I've learned one of the secrets that he was involved in this trial with magnets, which attributes why he has this magnetic personality.

I've been asked--and I want to thank my colleagues at CFSAN--to tackle the issue of *in*

vitro and animal models as they relate to human osteoarthritis, a somewhat daunting task, especially considering the audience. So what I'm going to try to do today is to give you a bit of a regulatory bent on some of these issues, so you'll see some slides that look familiar, but I'll talk about them in a different way. The bottom line, no pun intended, is what I'm going to try and do is give you some food for thought here.

In particular, what I'm going to try and do is establish the kinds of like that exist to the human situation and how solid these links are. So, for example, should some of these lines be drawn with dashes? Should they be making circles? And I want to make you aware of something that we haven't really talked about yet so far. For example, when we talk about animals, I've had the privilege of working with colleagues at the Center for Veterinary Medicine here at FDA, and one of the first times I went over there and gave a presentation, because I talk also about pain and OA with that group, is they reminded me--actually

reminded me that the animals that they take care of are their patients, which is something to remember. So they actually refer to them as "companions" and the person that brings them in as "clients." So I think we need to always keep in the back of our mind the distinction, potentially, when we're referring to animals. Are they companion animals or are they animals that are used in experimental models?

Then we talk about histology cells, enzymes. What are the links, how strong are the links? And I'll wander off a bit into some discussion of surrogacy because that really is, in essence, what we're trying to get at when we talk about links.

This is a very complicated issue, as you've heard. OA sounds simple on the surface, but I think you've gotten today--and you'll probably hear it from me again--that there are more questions than answers.

About four years ago, a little over four years ago, I had the privilege of being involved in

the Osteoarthritis Initiative, and I gave one of the opening--it was, in fact, the opening presentation, and this was one of my slides that I showed right off the bat: There are currently no FDA-approved therapies that alter joint structure in OA. And that is still true today. And I think that is, in essence, also true for our animal companions, for the most part.

So the thrust of that presentation at that point in time was that this needs to be changed. We need drugs out there, we need therapies out there, and that still is the case.

So when we refer to human OA, I just want to--and you've seen some of this already. I just want to make a few points. There are some estimates out there that, you know, it has a huge economic impact. It attributes for a large number of lost work days, either due to pain or loss of function; that there are a lot of people that have this, estimates here, for example, of 12 percent. The literature in the animal sphere suggests maybe it's even 25 percent of dogs, for example, have OA.

Results, in one estimate, in upwards of half a million replacements either of knees or hips in a year or so. It's a big problem. And this was a slide that I don't know where I borrowed the number from, but it's obviously, in terms of marketing aspects, a huge market.

So what are some of the questions then that are raised in general and might be raised as we think through and think about some of these risks and links? For example, is OA an inevitable part of aging? Well, there are certain people that think that certain joints in most people remain normal way into old age. So the answer to that seems to be, at least depending on what joint you're talking about, no.

What is the etiology of OA? And it's likely, as we've heard today, multifactorial and involves genetic aspects, developmental aspects. But something I'd like to concentrate on just for a bit today are the concepts of overuse--and we get into discussions, I think, of acute and chronic trauma in that regard--and then also the issues,

amazingly, of underuse, which can be something that can lead to atrophy, which I'll talk about a bit.

Something that hasn't been discussed so far is this concept of primary or idiopathic OA versus secondary. And as it suggests, primary is the cause is unknown; secondary may be related to overuse, for example. So another feature to keep in mind as we look for these links, or lack thereof.

FDA and CDER have a draft guidance out. It was first published in 1999. Here's the website for any of you that may need it. And this guidance is, to a large part, based upon the conceptual model, I think, that Dr. Simon presented, and I'd just like to reintroduce this just to make a few extra points.

As you read the document, it's based upon the idea that, you know, biochemical changes results in structural changes, and then this pain starts to show itself, and that is, in fact, when somebody has the clinical diagnosis of OA. And it also leads to functional limitations. Dr. Simon

has pointed out reduced quality of life and potentially, in the right patient, surgical replacement. Now, these with the asterisks here are all important outcomes to any particular patient, which is then important to us, because these are something that we can give approval for for a drug, for example, if you improve these.

Which leads me then to the discussion for a bit of surrogate approval, and were you to pick out and make the mistake maybe of reading the Code of Federal Regulations, going to 314.510, you would see, as has been alluded to already, that FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled trials establishing that the drug product has an effect on a surrogate endpoint--so this is then finally referred to as the surrogate approval or Subpart H mechanism for getting on the market--that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival

or irreversible mortality. Quite a mouthful.

Again, some of this was covered by Dr. Simon, but the way that surrogate endpoint is classically defined is that it's an endpoint of a clinical trial that defines a laboratory measurement, for the most part, or a physical sign used as a substitute for something that is a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Remember those asterisks that I showed you before. The idea then is that changes in any kind of therapy on a surrogate endpoint would be expected to reflect changes in the clinical endpoint as well. This is only valid if the effect on the surrogate leads to a clinical benefit. So we struggle a lot in trying to come up and understand these relationships on the drug side.

So it's probably safe to say then that surrogate endpoints can be candidates for drug approval. There certainly are some out there. But biomarkers do not have the same regulatory implication. So a biomarker, if it's doing its job

properly, will at some point be a surrogate, but not all biomarkers are surrogates. And this slide just simply reinforces that idea that there is this overall hierarchy leading to--which is what we're most concerned about, is some kind of a clinically meaningful outcome.

So if you look at the draft guidance for OA, there is a discussion that joint space narrowing--as Dr. Simon has already discussed briefly, is that joint space narrowing is viewed as a surrogate for structural changes, whatever that means. We generally ask that the trials be at least a year in length and that you also measure pain, patient global, various kinds of patient-reported outcomes, and then the issue of whether or not structure itself can stand alone, so let me just talk about that for a bit.

Actually, it is described in the guidance that were a therapy, whatever it may be, if it were possible to actually normalize the X-ray, that that could stand along as a claim. You wouldn't need to have any other evidence. Similarly, we talk about

the fact that if you were to improve the joint space narrowing over baseline, this would also probably be a stand-alone claim because that would suggest that there was new or regrown "physiologic" cartilage. And I think there's been some discussion about normal versus abnormal cartilage in that regard.

If you were to slow the joint space narrowing by a clinically relevant amount, then we would have a discussion about whether or not there was enough evidence that you would need some symptom evidence with that and, in fact, would you need some Phase IV studies to kind of help us understand what that meant. And if you can't define what a clinically relevant amount is for us, then you would definitely have to establish some kind of a link to a clinical benefit, and that's when joint space narrowing is then functioning as a true surrogate.

So this slide, as you just saw before, I just want to make a little different twist to this. In the matrix of hyaline cartilage--in particular,

this is hyaline cartilage--a lot of the thinking has revolved, at least as I understand it, that there's an important distinction to be made between collagen and the surrounding matrix in the sense that using this building as an analogy, were one to go at the drywall, for example, the walls, you could easily patch that if there was a problem. But were you to start taking down some of the actual steel beams and supporting structure, that's an entirely different issue. And so I think part of the discussion that we always keep in mind is, you know, what are we talking about here? Are we looking at something where the Type II collagen, for example, has been altered, and maybe irreversibly altered, versus looking at proteoglycans and glycosaminoglycans.

I won't belabor on this slide anymore. It's been discussed. I just want to make a point or two here. As you look down, I've just listed that, as we all know, the hemo cartilage is primarily water. Chondrocytes swim, in essence, in this kind of water with matrix. The matrix

consists of several different things. One of the things that has always impressed me is, for example, looking at glycosaminoglycans is chondroitin sulfate, the 4 versus 6 positioning on the sulfate. And when I was doing one of my post-docs with Robin Poole up at the Shriner's Hospital in Montreal, we were raising monoclonal antibodies, and it always impressed me how an antibody, how the body could pick out a 4 versus a 6 sulfation pattern exquisitely, I think pointing out the complications and the intricacies of what goes on at all levels.

So you have, again, seen this slide, and I just want to re-emphasize the point that cartilage, particularly hyaline cartilage, is really thought to be aneural, avascular, and alymphatic. So even if it's broken, it probably can't hurt. And so that brings us, as we've matured, I think, over the last couple of years, that the joint really should be viewed properly more as an organ and not just looking at hyaline cartilage, for example.

So let me just talk for a bit about some

of the issues surrounding joint space narrowing from the human perspective that might help you understand some of the other--the animal setting, for example, and there's been allusions to this, but let me just talk about it for a bit.

When you take X-rays of knees, there are various things that you can do, and one of the things that you can do is just stand there, as you see in the first slide, extended, and that has been how some trials in the past have been done and criticized for that. So there's been a major effort over the years to try and standardize taking an X-ray. It seems pretty obvious, but it's actually quite challenging.

One of those is the middle one, which says semi-flexed fluoroscopy, so in this instance, what you do is have the patient stand there and you use fluoroscopic techniques to actually position the joint, in particular, the posterior to anterior medial aspect of the tibia plateau so that it's parallel to the beam. And there has been an immense amount of work that's been done to

standardize this. So even taking something as simple as an X-ray isn't that easy. Imagine doing this in an animal.

So there are, as I have been discussing, issues in terms of standardization for X-rays, the idea that conventional X-rays are not reproducible, so the solution has been this Buckland-Wright technique, which I've just been describing, where you, in fact, can use magnification and use software to kind of analyze these things. But when you think about it, it actually kind of creates another issue. Yes, you have been very diligent in producing some results, but now can you reproduce these in the clinic? How many clinics take the time with patients to actually go through this procedure to find out who would be a candidate to take the therapy, whatever the therapy may be? So it's an interesting conundrum.

So let's turn to *in vitro* considerations, the topic that I was asked to talk about. And I won't dwell on this too long because I'm sensitive to time. But, you know, if you're going to do an

in vitro approach, there are certain very important considerations. We've heard that the chondrocyte is a very important cell. It's an often overlooked cell. It's kind of maybe the Rodney Dangerfield of, you know, "no respect" kind of cells. But it has a very important job. It maintains its matrix. It has to respond to its environment. It has to keep things in an equilibrium. And so it's very sensitive to feedback because it has to go through anabolic phases to produce proteoglycans and glycosaminoglycans, for example; it has to destroy its environment, so it has to go through catabolic phases, where it secretes things like matrix metalloproteinases, which I'll talk about in a bit.

These ideas are what have been used for a long time, but not as successfully as many would like, to kind of get at the issue of can we use what happens to the chondrocyte as it's responding to tell, number, one, what's going on. Is it in a catabolic or an anabolic phase? And do we change that with therapy? Are we getting, for example, more anabolic responses with something?

Then the *in vitro*, whatever the situation is, has to really, you know, kind of address the issues of cell-cell contact, cell-matrix interactions. It should really talk about, you know, and address the issues of loading stresses because, as we've heard, that's one of the ways that joints get their nutrition. It's by the constant loading and unloading as we walk along so it doesn't have its own blood supply. That needs to be taken into account. And even something as seemingly innocuous as temperature, for example, you know, core body temperature is 37, but there are estimates that at the ankle joint the temperature is 29 degrees. So what was the temperature where these *in vitro* systems were conducted?

So I'd just like to take one instance here, and I've kind of put together an *in vitro* and an animal with something that was in Biochemical Journal last year and just simply summarize some of the results which I think raise some of the issues which we're discussing today.

They point out in this paper that without glucose, glucosamine can certainly act as a sole source of glycosaminoglycans for the cell. But they go on to point out that when they add glucose to their system, it acts as a strong competitive inhibitor to the utilization of glucosamine to produce glycosaminoglycans, which is a problem. So you have to figure out how much glucose then do you have versus how much glycosaminoglycan in whatever system you have.

When you look at the glucosamine itself, these particular authors found that it didn't really stimulate production of GAGs. In fact, at the higher concentrations, it seemed to actually produce less GAGs, which seems to be a paradoxical result, but as we deal with surrogates on the drug side, we've certainly seen that certain surrogates do not do what they're supposed to do. In fact, some surrogates are dead wrong. But that's where the clinical trials can come in and help answer that.

So this particular paper goes on and

discusses issues about, you know, what are the likely levels of glucose or glucosamine in an environment and, you know, how can things get there. It has to go through--you know, the best way to a joint is through the mouth. So it has to go through the stomach, bloodstream, synovial fluid. You know, is it even feasible that things can happen? We've heard a bit of that discussion today. But I think what this does is points out some of the cautions that we need to always have in the back of our mind as we interpret *in vitro* results as they might apply to a human situation.

Turning then to animal model considerations, I'd like to focus for a bit on the issue of pain because, as we heard about, pain is what really makes the human OA what it is versus just some structural changes. But it's also very important for animals, and I'll talk about that in a second.

Other considerations are the various interventions which I'll talk about; the species differences, does the animal walk on four versus

two legs; differences in biochemistry; and then differences in underuse, which I'll talk about in a bit more detail.

So, pain. It's a four-letter word. We spent two days talking about this, almost two years ago already--I'm amazed. It took that long, and we could have talked easily for two more days. Pain is a very, very complicated topic, and I'm in the Division of Analgesics, so I can attest that it's complicated.

Now, when we talk about pain in terms of humans, one of the things that's very important, I think, to remember is that in human OA pain is studied and addressed and discussed directly by the patient. You ask the patient and they tell you. And we have, as you've seen--and I'll talk about a bit more--we utilize, for example, the WOMAC for lower extremities.

In an animal setting, however, this has to be done indirectly, and quite often it's done by veterinarians, for example. So in a chronic setting, they might look for lameness, which is an

issue looking at function. Or in a more acute setting, they might look, for example, is the animal vocalizing? What are his or her behaviors? Eating, activity level? And, in fact, they even talk about physiologic changes that may occurs in terms of, for example, pulse or blood pressure. But this is a very important distinction because it's difficult to get at the issue of pain then because you can't get at it directly.

So were you to come to our division and you wanted to be approved for the treatment of osteoarthritis for treatment of signs and symptoms, we would ask you to look at the following three co-primary endpoints: pain, a functional assessment, a patient global. And we would ask that these trials be done at least for three months.

We would encourage you to employ the WOMAC pain index. As you can see here, it has pain--it's not just a simple question, How is your pain? It's actually five questions, and as you can see, they ask different kinds of questions: pain walking on a flat surface versus pain lying versus pain

standing and at night. And I think this gives us a richer idea because we still don't understand in terms of what causes directly pain in any particular joint. This gives us a bit of a more robust assessment to what's going on when somebody says they have pain.

Now, turning then directly to the animal models, I just made a few slides to list a few things here to make some points. So there are, for example, chemically induced models where you intra-articularly inject things like iodoacetate or enzymes like papain, chymopapain or collagenase. What you're really trying to do here and I think the thinking has been to create some kind of a toxic situation to the cell. You may induce, for example, some kind of inflammation. You're trying to set up a system that you can study. I think that there is a general movement away from these kinds of setting recently because they are, to some extent, maybe not really very reproducible and don't really tell us much about the situation either in humans or animals.

There are then more--the models that have been studied in a bit more detail, as far as I can see, are those that are physically induced: the anterior cruciate ligament transection model, for example, using either one or both knees in the dog or the rabbit--Dr. Altman had talked about this, for example--or the meniscectomy models in the rabbit and guinea pig; immobilization in rabbit or dog; or the patellar contusion model in rabbits. I'll talk a bit more about one of these in just a second.

Then there is something here that I have listed as spontaneous models of OA, and this seems to be where things are generally going in the field because it maybe mirrors better the situations that we're dealing with today. So, for example, the Hartley guinea pig many feel gets at the issues of age and obesity better, and then what I've listed here as genetic approaches. There are some that have been studied that have unidentified genetic defects, whereas others have been actually targeted in, for example, in Type II and Type IX collagen.

And then I guess I would argue that the hip dysplasia in dog is also a genetic model because it seems to follow in more pure-bred versus mixed-bred animals. Again, I think this is really where these animal models are going these days.

So let's just talk for a second about the cruciate-deficient dog model and some of the lessons that we seem to have learned from this setting. One of those is that chondrocytes can repair their damage, as we've heard about, and this leads to hypertrophic cartilage with increased glycosaminoglycans. This seems to be true in humans, in rabbits, and in Rhesus monkeys, for example. There is also this idea of what's been called neurogenic acceleration where you take and you actually do a dorsal route ganglionectomy, for example, to accelerate the damage so that you get more observable damage during your trial period. But there are many that feel this is not a good representation for, again, consideration of a primary or idiopathic OA. And some of the arguments go that, you know, the homeostatic phase

of this hypertrophic repair, if you use just the neurogenic acceleration versus just a cruciate ligament it's different. So you're really looking at kind of different things, and it's hard to make comparisons.

Then as I talked about and alluded to earlier, the importance of periarticular muscle, if you immobilize the joint, this can lead to atrophic changes of glycosaminoglycans. To what extent this may mimic, for example, what Dr. Brandt often talks about is quadriceps weakness in elderly women and that, in fact, this may be in and of itself a predisposing condition to human OA, not a result of.

So I'd just like to give a short example here of something. This is just such a colorful slide, I couldn't, you know, not put it in. It just points out--this is a slide showing the various domains of the matrix metalloproteinase family. It's not meant to be complete. It's just meant to show that there are several members to this family. And so there have been efforts over

the years to go after this as a target with evidence, for example, that MMP inhibitors in osteoarthritis, they hydrolyze the relevant kind of substances that we've been talking about, for example, the proteoglycans and such, that they're upregulated by disease mediators, such as we hear Dr. Abramson in the interleukin-1, for example; that if you look into *in situ* hybridization techniques and immunofluorescence, it seems to be at the right place where degeneration is occurring; that you can get actually characteristic signature cleavage fragments *in vivo* that can represent this dichotomy I was talking about before of anabolism versus catabolism; and that these are blocked by natural compounds, for example, TMPs, but also by selective inhibitors.

So one of the things that is important, again, to remember is that we're not all the same, we differ. And as you look, for example, here, under Collagenase 1, I just listed that as far as I know--and I would love to be correct, but as far as I know, there are no similar enzymes in the rodent

model of a rat or mouse. So there are always some differences between species and humans to be paying attention to.

There was a trial, some trials a few years ago where they were looking and utilizing the rabbit meniscectomy model with therapy which I've just anonymized here as Therapy X, and it has three different concentrations. And they had various parameters that they were looking at: fibrillation, fissures, erosions, and global scores. And they did the proper kind of experiment with normal and a sham and then a vehicle control. And as you can see, as you look particularly look under the 10 mg/kg/day group, some of the changes from the vehicle, for example, appear to be quite dramatic, and, in fact, some of those have reached significance, as I've indicated here.

If you look in another model, in the dog cruciotomy, again, with the same low dose and high dose of this particular therapy, as you look either at the area of the lesion or a composite assessment of the lesion, again, the data certainly suggests

that at the high dose there is some improvement here.

Well, unfortunately, these haven't all panned out. The idea is that, you know, when you talk about OA and structure modifiers, the idea is that you can limit joint damage. And I think it's pretty safe to say at this point in time, at least in human OA, when we look at things like MMP inhibitors, for example, there's no demonstrated effect in RA or OA. Some of these in the literature, these trials have been stopped because of safety concerns. And, interestingly, some of the problems have related to somewhat unexpected findings in terms of stiffness and pain in things like shoulders and hands.

Looking at bone, for example, there were some discussions briefly here already about bisphosphonates, and there have been some suggestions in Phase II trials that they could be effective, but at the most recent ACR meetings, the Phase III trials were not shown to substantiate this. So my original slide back in 2000 is still

true.

So as I end here, I'd just like to bring up a few points that might be of use for your consideration, and I've drawn a comparison here between RA and OA.

In RA, we have many new compounds that have entered the market, and they have demonstrated either a clinical benefit before or after drug approval and structural benefit before approval. And some of the clinical benefits that have come later has been looking at longer-term, more robust endpoints, such as patient's function, for example.

In OA, as I said before, we have currently in the human setting only drugs for a clinical benefit, meaning pain reduction, for example. So were we to look then at structure modifiers, how do we approach this? When, for example, if we look at a clinical benefit alone, would we want that to correlate with a structural benefit, before or after therapy? And that is, in fact, where the discussion has come in in terms of looking at these compounds for what might be a Subpart H type of

approval.

Now, I think there's been a lot of learning that has gone on over the years about joint space narrowing, and I think we continue to learn. I've just illustrated here something to think about. For example, I think not too long ago, it might have been fairly straightforward and agreed to that there's a trajectory here for somebody who demonstrates rapid loss of joint space narrowing versus somebody who's on this kind of trajectory, which is slow. But, in fact, it may be that it isn't quite so simple and that, in fact, in any individual patient it may be that it's a combination of these two features. So that, for example, somebody may be on a rapid course for a while, and as we've heard, the body attempts to make some repairs and, in fact, is successful. But then things pick up again. And as you think this through, whenever you might take a snapshot with your X-ray looking at joint space narrowing, one has to always consider how much this might factor into the results that you get, or lack of results.

One of the ways that we've struggled with this issue about what should be the endpoint is to try and come up with something called the virtual joint replacement endpoint in OA. And this is really an effort to kind of standardize development because we're sensitive to the fact that not all health care systems across the country and across the world are the same. So we've been wondering with colleagues if we could come up with an agreed-to standard, a composite endpoint, for example, of pain function and radiographic endpoints, that might allow us to look at the time to a virtual endpoint of joint replacement, again, getting at this idea of function and--I'm sorry, of survival as an important endpoint in OA.

So just to wrap up, I think we've gotten a lot of instances here that osteoarthritis is considered nowadays to be an organ. It's a very complicated organ and much to be learned, but as we look through here, you'll notice that I've drawn--everything else has an arrow, for example, going to pain except cartilage. So whatever happens in

cartilage seems to act indirectly through other mechanisms to lead to pain, which then leads to these other clinically important features. Somewhere down here versus somewhere up here there's a transition from a biomarker to a surrogate as it becomes more looking like a clinical endpoint. And then we wrestle, along with a lot of others, in terms of where can we actually demonstrate these kinds of relationships, these links, as I've talked about before, and establish those. Is it in Phase I, II, or even Phase IV trials?

I'd just like to end with part of a sentence from a recent paper from Dr. Brandt. Although he was talking for the most part about therapies, I think this is useful for our discussions today. He says that, "The validation of a molecular target in human disease can be obtained only after positive results are obtained in Phase II clinical trials in humans." So I guess maybe the only way that we really can hit the mark is to study the mark.

Thank you.

DR. MILLER: Comments or questions?

DR. ABRAMSON: Steve Abramson. Jim, I'm just curious about this surrogate endpoint, the H. Apropos of Ken Brandt's comment, which I think was very important, do you envision that there will ever be a surrogate marker where there hasn't been good data, at least with a preceding medication for Phase III effects on that surrogate marker? I'm thinking of serological tests in lupus as an--I'm just trying to think of ways that one can justify using a surrogate marker when there has not been good data affecting that marker, gives a good clinical outcome.

DR. WITTER: Are you asking just in general terms?

DR. ABRAMSON: I'm curious about this H pathway, especially after all the discussion on structure modification in osteoarthritis where there has always been the notion, at least up until now, about needing to have some symptom benefits.

DR. WITTER: Right, right. The essence of

a Subpart H approach is that at some point in time you will have to demonstrate that there is some clinical benefit, whatever that may be. And we have not specified necessarily what that clinical benefit has to be, for example, if it's pain, if it's improved function, if it's time to less need for joint replacements, for example. But the idea of surrogates is that you could be approved, on the market, but validation of that surrogate endpoint would have to then come with due diligence, with adequate and well-controlled trials. There are caveats here that, you know, a Subpart H track, for example, might be viewed in simplistic ways as a quick way to get on the market, but it also is a quick way to get off the market if things aren't validated.

I don't know if that answers your question or not.

DR. MILLER: Other comments or questions? Dr. Lund?

DR. LUND: Just to show my ignorance here, nobody has mentioned TMJ. Is there anything in

this having to do with jaw and jaw diseases?

DR. WITTER: Well, I actually work with Ray Dionne, who is the Dental Institute here at NIH, and we often wander into the discussion of TMJ. It's a very complicated setting, as you might imagine, and there has been a lot of renewed interest to look at that as a useful model for OA in general. So it has not been overlooked, though.

DR. MILLER: Dr. Harris?

DR. HARRIS: I'm not quite sure how to phrase this question to you, but it's just something that is very confusing to me, and that is, when we are talking about the biosynthesis now of the whole matrix component, we're talking about many different factors, including the collagen Type II and then those glycosaminoglycans that you mentioned the chondrocytes are able to make. But do we have any evidence that once we destroy the collagen we're able to reconstruct the matrix? And could that be an irreversible step here?

DR. WITTER: We have colleagues in the room that can answer that as well, but my general

understanding of the literature is that that is the case, that once collagen begins that cascade, that is the beginning of the end for that joint.

DR. LUND: Does that mean it cannot be repaired or reversed?

DR. WITTER: In repair or reverse, yes, I think that's generally a fair statement. And then I think--was it Dr. Lane who had brought it up before?--this idea of the repair aspects may not then be the right kind of collagen, that it can't withstand the stresses and such. So, you know, it's--the term has become important. Although it may be repaired, it may not be the right kind of collagen. It's not laid down properly. It doesn't function properly.

DR. MILLER: Jean?

MS. HALLORAN: We heard that crystalline glucosamine is approved as a prescription drug for treatment of arthritis in Europe. Is there a reason why it hasn't been approved in the United States or can you comment on that?

DR. WITTER: Probably not. I'd better

not. There are others that can comment. I won't.

DR. MILLER: Okay. Thank you.

We'll take a break for 15 minutes. Be back here at 3:15.

[Recess.]

DR. MILLER: For the remainder of this afternoon, we're going to deal with an open meeting, open public hearing. Individuals who wanted to make statements to the committee are invited to do so, having made a request to the FDA prior to this meeting. We have five such requests, and we will have these individuals in just a moment. But I have been asked to read this statement prior to the meeting concerning the openness of the hearing.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an

individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or group that's likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payments of your travel, lodging, and other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The first presenter is Dr. Jason Theodosakis of Cargill. Dr. Theodosakis, you have seven minutes.

DR. THEODOSAKIS: Thank you very much. I'm not with Cargill. They paid for my trip here. I'm not an employee of Cargill.

Here are my disclosures. I'm hoping to have a second page because the more you have, the less biased you are.

I think the presentations have been excellent this morning. I would have changed my presentation based on what has been presented so far, but basically I think osteoarthritis is underestimated. This is a recent radiographic study on 55-year-olds and older, mostly women, and they found 96 percent had radiographic evidence. So OA is real common. CDC keeps upgrading the percentages in the public, and as we get fatter and more diabetic and older, I'm sure this is going to increase.

Our current treatment of NSAIDs are not disease-modifying, and, in fact, as more and more evidence comes out, the treatment with NSAIDs appears to be more and more toxic, leading to blood pressure, congestive heart failure, and possibly an acceleration of the disease.

Often, people quote the Singh study that says 16,500 people a year are dying from

complications from NSAIDs, but this was published back in '98. And if you look at the assumptions, we have new evidence to say that this number, which is 45 deaths a day, may actually be quite a bit higher, especially since we found an interaction, for instance, between Ibuprofen and aspirin that may reduce the cardioprotective effect of aspirin, as well as many other issues. So I think the need for this conference is very timely, and I'm glad that everybody is putting so much effort into it.

The other thing that I saw today is that this is such a variable disease and so difficult to study that we really should look at all the data. And I'm not sure if I agree, but just looking at Phase III clinical trials, because we have indirect measures and there's all kinds of problems with the study which have been well delineated. But if you look at the whole data, that's the way to make the decision. It could be argued even that animal data looking at gross and histologic and grading the cartilage before and after treatment with the supplements might be a more precise measure of

what's happening with the supplements rather than the indirect surrogate measure of pain and function scales or even X-ray.

The outcome measures are real interesting as well, and there are three studies that I've noticed with chondroitin, for instance, that say, Hey, what does this do to society? If in France we give chondroitin to people, how does this affect cost? How does this affect NSAID consumption? And the outcome measures are also important. This particular study of 11,000 patient records found that 50 percent of the people that were using NSAIDs for osteoarthritis were able to stop completely on 1200 mg of chondroitin, and the average reduction was 67 percent. And even though chondroitin is expensive, the net cost was zero because there was decreased physical therapy visits, complications related to NSAIDS and so forth. And I believe there are two other studies that have even better evidence to show that there's a cost savings.

There's some talk about glucosamine

sulfate versus glucosamine hydrochloride, and the issues I wanted to bring up are the following: these are salts, and the salts break apart in the small intestine with a high pH; you have an uncharged molecule that then can pass through membranes easily, and this is probably what gets to the chondrocytes where all the action occurs. Some of the early basic science and even the pharmacokinetic data was done with radiolabeled glucosamine hydrochloride. And there are essentially two studies now that I've noted that have a comparison between HCL and sulfate, and when corrected for molecular weight, they were equivalent in proteoglycan synthesis. Interestingly, the N-acetyl-glucosamine was not as effective.

Another study suggested--this is a basic science study on equine cartilage explants--that it is indeed the glucosamine and not the sulfate that is the active component, and glucosamine sulfate and hydrochloride were similar in terms of the outcome measures in basic science experiments.

Other people point to the negative studies on glucosamine HCL and say, Hey, we have these negative studies, that means glucosamine sulfate is probably more important. But these studies really have to be looked at with a grain of salt. One study was very short, eight weeks in duration. The subjects in the study had a higher level of more advanced disease, Grade 4 K&L. And they were allowed to take NSAIDs ad lib, and so it's sort of like doing a study on Advil when the people are allowed to take Aleve with it. You know, we should be careful in reviewing those negative studies.

A study by Lou Lippiello looked at animal histology in rabbits and found that indeed glucosamine hydrochloride and chondroitin sulfate both were effective at reducing the lesions in the rabbits histologically when pre-treated, and the combination had a better effect than either one alone.

With chondroitin, the effective dose, several studies now show 800 mg. People have said that, well, it's probably not absorbed so it

couldn't be effective. But there have been pharmacokinetic studies with it, and you have to look at all the double-blinded studies. They're all positive, in addition to the outcome study which I earlier alluded to.

The largest study so far, disease-modifying with either supplement, is 800 mg of chondroitin sulfate, and this showed not only a significant difference between the placebo but minimal joint space actually significantly increased in the chondroitin group over a period of two years using flexed X-ray positioning guidelines.

In summary, I think we look at all these studies and we have to realize some key points. You need all of the evidence, not just the placebo-controlled trials, because of the heterogeneity of the disease and all the implications in doing the research. And we are studying people with primary OA, and the folks out in the public have a lot of secondary OA. I haven't seen any studies of this, but clinically I've seen the most dramatic response

in people with crystalline disease, pseudogout and gout. You know, it would be great to look at this.

Glucosamine hydrochloride and glucosamine sulfate and chondroitin sulfate I think would be a big benefit to the public in reducing overall morbidity and mortality from our current treatments and reduce the costs overall of treating osteoarthritis in society.

Thank you very much.

DR. MILLER: We have time for one or two questions.

[No response.]

DR. MILLER: If not, thank you.

The next speaker is Dr. Gayle E. Lester of NIH. You have seven minutes, Dr. Lester.

DR. LESTER: Thank you. I appreciate the opportunity to come to speak today, and I have just a few comments to make initially about some of the problems associated with the extrapolation of data generated from animal models to human disease.

Dr. Witter has really covered this very extensively in his presentation and has described

for you the numerous animal models of OA that exist, and these include both spontaneous and induced disease.

While these models present opportunities to explore changes in articular cartilage and associated joint structures, each one has its strengths and weaknesses. Many agents show protective effects in animal models, but the predictive value for human OA remains somewhat obscure.

Whether or not these models accurately reflect disease risk factors sufficiently to indicate prevention and prophylactic actions of agents really remains to be shown.

In an effort to identify better biomarkers for OA to help facilitate clinical trials and drug development and drug discovery, the NIH has recently launched a large clinical cohort study that I'm going to spend the rest of my time talking about today.

The study has been referred to several times this morning, and I appreciate the

advertisement. I'm the project officer for this very large contract, the Osteoarthritis Initiative. The goals of the Osteoarthritis Initiative are to create a research resource to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for OA.

The mechanism we chose for this--and this was done through collaborations. Dr. Witter, as he told you, was the introductory speaker for our first session; Dr. Felson, Dr. Abramson, Dr. Altman, many people have been involved in this process over the years--was to develop a prospective natural history cohort of individuals with early OA and with risk factors. So this is here the definition of what we've been talking about today. How do you define when the disease starts? And this is what we're hoping to try to capture in the Osteoarthritis Initiative, the early phases of osteoarthritis development.

This will be a natural history cohort study, no treatments, and these individuals will be followed for five years. We're going to be

collecting clinical information, a WOMAC assessment, functional assessment, physical exam, dietary supplements, treatments that these individuals might be using. We will have an extensive database of MR and X-ray images and biospecimens as well.

This is a public-private partnership that is funded through government and private partners, and you can see from this slide that we have many NIH Institutes involved in this, as well as three pharmaceutical partners who have chosen to work with us to move forward the area of biomarkers for OA.

The particular individual academic centers involved in this study, the clinical centers are the Ohio State University under the direction of Dr. Rebecca Jackson; University of Maryland under the direction of Marc Hochberg; University of Pittsburgh under the direction of Kent Kwoh; and the Memorial Hospital of Rhode Island under the direction of Dr. Charles Eaton. All of these are coordinated under the University of California-San

Francisco center run by Dr. Michael Nevitt.

The research resources from the OAI should, we hope, stimulate basic research on biomarkers, facilitate drug development through the identification of biomarkers of disease onset, identification of biomarkers for disease progression, which we've heard today may be quite different, and elucidation of the basic disease processes and risk factors.

The long-term results from the OAI may include a more thorough understanding of OA and its manifestations in at-risk populations; positive interactive relationships between the parties involved, that is, companies, academia, and the government; and more efficient and safe assessments in clinical trials.

And I'll also mention at this point that there is also a very large similar study being carried out under the leadership of Dr. David Felson, the Multicenter Osteoarthritis Trial, the MOST study, that will generate similar data.

So although we don't have it now, we're

very hopeful that within three to five years there will be a very rich database, and one of the things I didn't mention is that this resource will be public and will be available to investigators throughout the world for their own investigations and hypothesis testing and data mining.

I thank you for your attention.

DR. MILLER: Thank you, Dr. Lester.

Any questions or comments for Dr. Lester?

[No response.]

DR. MILLER: If not, thank you.

Our next speaker is Dr. Robert Arnot, network news correspondent, who will explain mechanical and chemical changes in joints that evolve from initial joint tissue insults or injuries to full-blown osteoarthritis. You have 15 minutes, Dr. Arnot.

DR. ARNOT: Good afternoon. I am a physician. I am a journalist. I have reported for the last 20 years for three different networks on osteoarthritis as well as a variety of other diseases, spent the last year and a half in Board

of Governors with the 1st Marine Expeditionary Force and various components of the U.S. Army, and I am glad to be back here in Bethesda, Maryland.

Also, my only financial stake in this is that I am the author of a book called "Wear and Tear Arthritis," and I have a very personal stake in this book. I wrote it because I was diagnosed with severe osteoarthritis in my right hip. I have osteoarthritis of both of my knees. And I was on 12 to 16 Advil on a regular basis. I was unable to really bend over to play with my then-six-year-old, unable to play tennis or ski or do any of the things that I wanted to. And I really embarked on a course to see what I could do in terms of preventing any further deterioration in my own condition.

Now, we have heard a lot of evidence here this morning and this afternoon, and it does kind of tend to pile on. We in the news media and as physicians tend to look at one clinical study, one watershed event, that more than any other really changes clinical practice. I know many of you know

this study from Lancet, but I just want to very briefly review it because this is the study that physicians that I routinely run into at Stanford, at Harvard, at Johns Hopkins, across the country, use as their basis for treating their own patients with osteoarthritis and for trying to prevent those who may be at risk of osteoarthritis.

Now, as you know, there were 212 patients with knee osteoarthritis who were randomly assigned 15 mg of oral glucosamine, or placebo, once daily for three years. There were weight-bearing X-rays that were done, anthro(?)-posterior radiographs of each knee in full extension, taken at enrollment and then one and three years later, also looked at symptoms.

Now, what we know if we look here is this: 106 patients on placebo had progressive joint space narrowing with a mean joint space loss after three years of 0.31 millimeters. But look at what happened in those who were treated. In those 106 patients, there was a loss of 0.06 millimeters. That's basically statistically insignificant; in

other words, they had little real loss.

When you look at their WOMAC score, the symptoms worsened slightly in the patients on placebo, and there seemed to be improvement in those who had glucosamine.

So, again, this is the study that we reported on the "Today Show" with Katie Couric. It's a study that we used on "Dateline NBC," really is that sort of watershed event.

Now, I think in looking at the problems before the panel today, the biggest one seems to have to do with this idea: Is this a suitable biomarker or isn't it? When you look at the loss of cartilage, I would put to you this is as good a biomarker as cholesterol or as good a biomarker as bone density.

I will just read to you--the FDA seems to have already decided this issue on its website, and it says that, "The FDA in its tentative conclusion states that biomarkers are parameters from which the presence or risk of disease can be inferred rather than being a measure of the disease itself.

In conducting a health claim review, the FDA does not rely on a change in the biomarker as a measurement of the effective dietary factor in a disease unless there is evidence that altering the parameter can affect the risk of developing that disease or health-related condition."

Now, this is the case for serum cholesterol in that high levels are generally accepted as a predictor of risk for coronary heart disease. I would argue it would be pretty hard to dispute that the losing of cartilage, that the lesser amount of cartilage puts you at higher risk of a bad event.

Now, for those of you in the FDA who look at drug trials, you look at coronary heart disease, and what you would say is you are not really looking--you have no markers of disease except bad events. Does someone have a heart attack? Do they die? Do they have to have angioplasty? Do they have to have bypass surgery? And it's very much the same thing with osteoarthritis. You have bad events. The bad event can be bone on bone,

osteoarthritis with severe pain and disability, and the need for a procedure, and, of course, that procedure would be joint replacement. So I would argue strongly here that this is a very powerful biomarker.

The second problem area has to do with what's the point at which a patient is actually diagnosed with osteoarthritis. Take, again, coronary heart disease. You can have somebody absolutely packed and loaded, look at their coronary arteries, look at the (?) thickening here. They can have all kinds of unstable plaques and up and down their left anterior descendant, and yet they are not diagnosed with coronary artery disease. Why? They have no symptoms.

So I think when you look at the burden of the disease there and the ability with coronary artery disease to say that you have prevention if you have fewer events, you're allowed to do, I would gesture, or certainly claim with osteoarthritis.

Now, here's the key point: I know that

the FDA has been very concerned that in this Lancet study, it would say, well, gee, they already have disease. The fact is, well, what do you mean they have disease? The key thing is that X-ray changes precede the clinical diagnosis and precede the onset of symptoms in most people. Take those over 60. In those over 60, about one-third of patients have symptoms, yet the vast majority or almost all already have changes on their X-ray. That means that the majority of patients are not formally diagnosed with osteoarthritis.

The great difficulty has been that right now today there are millions and millions of Americans who are chewing away at their articular cartilage and yet they are not diagnosed with osteoarthritis.

Now, the third difficulty seems to be the diagnosis of osteoarthritis. What I did in my book was to look at sort of three different phases. Phase one was what I call wear and tear, pure mechanical destruction of cartilage. In England, they actually divide the disease into two phases.

They have osteoarthrosis, which is going to be the mechanical grinding away of cartilage, and then you have osteoarthritis, where you actually have chemical changes that further degrade the cartilage, such as the increase in metalloproteinases.

As many of you have indicated, and my colleague from the NIH, there really isn't any marker to sort of say you have made that transition from the chewing away of cartilage to the point that you actually have osteoarthritis.

So when you look at what is prevention here, I would argue that if you are preventing events such as the replacement of joints, if you are preventing events such as the bone-on-bone sort of end-stage disease here, you are, in fact, preventing disease. And if you take myself, I went from taking those 16 Advils a day to taking none. I do take the glucosamine and chondroitin sulfate on a daily basis here. I have this as a regular program of yoga and joint strengthening. I was told four years ago that I would have to have a

joint replacement. I have not had that joint replacement I was supposed to have had. I am now completely pain free, back to playing tennis, back to downhill ski racing, and after, feel terrific.

So just to summarize these points here, the diagnosis itself, most people go undiagnosed; therefore, I guess you could say they don't have disease. And yet if you were to take an X-ray, you would see that there already are changes there. Those changes are probably mechanical. They probably don't already have any of the biochemical changes of osteoarthritis. And if you can at that point basically intercede and decrease the amount of cartilage that they have lost, you are going to be preventing events. Just like in coronary artery disease you are preventing a heart attack or you are preventing the procedure having to be performed, such as PTCA, here you are preventing these critical events.

Now, the other part of this in terms of evidence-based medicine is, well, what about the risk/benefit? I say to physician friends of mine

and they will say to me, I give this to somebody in terms of trying to prevent osteoarthritis or someone who actually has osteoarthritis. What's the downside here? The downside is that they, by being given these supplements or these nutrients here, don't end up having a fatal bleed. And they may not end up with further destruction of their cartilage.

So in terms of risk/benefit here, let's look at a study by Rush Presbyterian in which 53 subjects with symptomatic, radiographic evidence of wear and tear arthritis of the knee were studied. They took acetaminophen to relieve their pain. When the gait was analyzed, those with decreased knee pain tended to decrease the load on the degenerated portion of their knee. Loading the worn and torn cartilage with forces high enough to do further damage.

In my book, I took the strong stand that standard pain relievers, the NSAIDs that many patients have--and I tell my own 90-year-old mother this--that the likelihood is that they are

disguising some of their pain and that they are continuing to accelerate the damage rather than retarding the damage.

When you look at risk, acetaminophen over 4 grams a day, you do run the risk of liver toxicity, and although, of course, it is linked to alcohol intake as well, you do run the risk that you will need a liver transplant. Most physicians, including those at the BU Arthritis Center, would say that this combination, these nutrients are incredibly safe compared to any of the standard NSAIDs. As my colleague here, Dr. Theo, said, you are looking at 16,500-plus deaths a year, many of those with patients who have osteoarthritis.

Now, in the end, you would say, well, fine, if you get to make the claim that these nutrients can be used for prevention, who ends up taking them? Well, the interesting answer is those people who on a daily basis are grinding away at their cartilage, and those would be individuals who have, like myself, a high cavus foot, those who have a hypermobile foot, those who are knock-kneed

or bow-legged, who have a pistol grip hip, and anybody who has had an injury; for instance, my young niece who has an ACL injury, myself with a meniscal tear, those with injuries, those who have what I call fatal flaws; the tens of millions of Americans who are overweight, who pound as they walk around, are all doing damage to their joints.

For all of these individuals, the bottom line is that there is no preventive effort. Here you have a disease that may cause more disability than any other, that when you look at it outside of a stroke in terms of the cardiovascular disease, compared to cardiovascular disease, it's almost the same as having an MI when you have bad osteoarthritis of the hip. And yet there's absolutely nothing on a national level being done to prevent osteoarthritis, nothing in the way of yoga or strength training, nothing in physicians' offices, no agents that are currently being recommended as a way of preventing this disease. So it's a huge black hole compared to osteoporosis, coronary artery disease, cancer, and yet a disease

that basically is going to affect every single one of us.

I know a lot of my time is ending here. I know that you also don't like personal anecdotes, but I'm certainly a testament to the fact that this has worked and worked well. But I would argue strongly that, first of all, there is a real problem with the definition here of osteoarthritis, that I'm a strong believer you have a progression from wear and tear through osteoarthrosis to osteoarthritis, and at that point that you may see X-ray changes before you have actual symptoms, before a doctor is going to make a diagnosis, that you can intervene, you can intervene in a highly effective way to prevent events that are highly disabling.

Thank you very much.

DR. MILLER: Any comments or questions?

[No response.]

DR. MILLER: Thank you very much.

The next speaker is Dr. Jose Verges from Bioiberica S.A., Barcelona, Spain. You have ten

minutes.

DR. VERGES: Good afternoon. First of all, I would like to thank the Chairman and all of the panel of the FDA to give me the opportunity to speak at the meeting here in Bethesda. I am a clinical pharmacologist from Barcelona, and for me it's a great pleasure to be here at the FDA. It's a big dream for a clinical pharmacologist to have a meeting with the FDA. That means that I am very happy.

Secondly, I understand that you are very tired of speaking all day about chondroitin and glucosamine and osteoarthritis. I would like to be very precise. Also, a lot of things during the day (?) , but some of the points that I have here we speak during the meeting, no?

Chondroitin sulfate is a symptomatic slow acting drug for osteoarthritis in Europe, where it has been approved as a drug for more than ten years in several countries in Europe. Personally, I am working for chondroitin sulfate and these kind of problems more than eight years.

Some of the mechanisms of action of chondroitin sulfate, you know, this morning were very well pre-(?) . I can state that on Friday we'll be presenting to EULAR, in the European (?) in Berlin two new mechanisms of action of chondroitin sulfate that we performed in my department together with Professor du Soich in the Faculty of Medicine in Montreal in the Department of Pharmacology. And we see that chondroitin sulfate can make the addition of stromelysin, metalloproteinase 3, that is very active in terms of inflammatory diseases. And another interesting thing is that the protein NF-kappa beta, that is one protein that it's very implicated in some process, especially in chronic treatments.

If we see the clinical trials that we perform for our company, I can tell you that Bioiberica is the first producer in the world of chondroitin sulfate. All of the clinical trials that have been published in Europe is our chondroitin sulfate. That means that we know something about our product. Nine randomized,

controlled clinical trials have been conducted in Europe with our product, comparing its effect against placebo and sodium diclofenac 150 mg in more than 1,000 patients with knee and hand osteoarthritis.

The results from these clinical trials conclude that chondroitin sulfate is as effective as diclofenac and around 50 percent more effective than placebo in the reduction of symptoms of osteoarthritis. This is very well published. We published recently with Professor du Soich in the Clinical Pharmacology (?) that the effect of chondroitin sulfate should be more than 50 percent than placebo. We published that the placebo effect is more or less in knee osteoarthritis of 26 percent. That is very important when we compare with placebo to know exactly which is the efficacy of placebo in knee osteoarthritis.

There is some evidence that chondroitin sulfate can stop the (?) process. We have three clinical trials in knee osteoarthritis that have evidenced stabilization of joint space width with

chondroitin sulfate treatment in comparison with placebo in the knee, and also we have two clinical trials in hand osteoarthritis, concluding that we have the possibility to stop the (?) process in fingers. This is published by the group of Verbruggen in Belgium, and it's a very interesting paper. That means that there is some evidence that chondroitin sulfate can stop the (?) process.

But it's very important to keep in mind that in Europe, chondroitin sulfate is approved as a symptomatic treatment for osteoarthritis. That means that it relieves the pain and improves the mobility of the joints. This is very important to know.

Another important issue is the safety. For physicians, it's very important because normally the people that have osteoarthritis are elderly people, and they have other pathologies. They have hypertension, (?) , and it's very important, the safety of this product.

The safety of the drug is very well documented. It's equivalent to placebo and much

higher than other anti-inflammatory drugs like diclofenac. One of the things that we proved is that chondroitin sulfate is not metabolized by enzymes from cytochrome P450. What does that mean? That means that if you give the product with other drugs, we don't have any kind of interaction with other products. That means that you can combine chondroitin sulfate with other drugs, with analgesics or hypertensive drugs, et cetera, and that is very important because there are a lot of interactions that could be a big problem for the patient and for the doctor. And that's one of the interesting things about this kind of product, they are very safe products that you can prescribe together with other drugs. This is a very interesting thing.

The pharmacosurveillance data from Europe, where no serious adverse events have been reported for more than ten years, support the safety of the product. We can say that in my department we have the pharmacosurveillance, and more or less we treat three million patients per day. That means that

it's a very important number of patients. That means that it's the best--the best clinical trial is the pharmacosurveillance, especially in Europe (?) , that is very, very serious, the pharmacosurveillance, how we can control the side events. That is a very important issue of this kind of product, glucosamine and chondroitin sulfate, the safety.

This is the recommendations of the EULAR that was published recently in Annals of Rheumatic Diseases, and you will see, for example, the level of evidence of chondroitin sulfate is 1A. It's superior, for example, to paracetamol and other anti-inflammatory drugs, for instance, and I think it's very interesting to note these data. In terms of the level of evidence, it's 1A, and its strength of recommendation is A. That is the maximum category (?) in Europe.

What are the benefits of chondroitin sulfate for patients and for doctors? I think chondroitin sulfate's clinical efficacy on symptom reduction and improvement of functional capacity,

that is clear. There is one interesting thing that the chondroitin sulfate has a carryover effect. That means that when you finish the treatment, in some patients they efficacy persists during some weeks and some months. That is very interesting for the (?) of the patient. Another very interesting issue is the pharmacoeconomics issues. We performed recently in Spain--that is my country--we performed a pharmacoeconomics study, and I will tell you that with chondroitin sulfate for 10,000 patients, we can reduce the cost of more or less $2 million for 10,000 patients (?) the reduction of analgesics, anti-inflammatories, and also the side effects for anti-inflammatory drugs. That means that from a pharmacoeconomic point of view, it's a very important issue.

There is only one chondroitin sulfate approved as a drug in several European countries, which is therefore considered as the reference product. This chondroitin sulfate is manufactured by Bioiberica and marketed in Europe by IBSA and Bioiberica, and in the United States by Nutramax

Laboratories under the trademark Cosamin.

This chondroitin sulfate is being used by the NIH study for its Glucosamine/Chondroitin Arthritis Intervention Trial. Its number is--well, this is the number. That means that we have an inspection from the NIH to our company in order to put our chondroitin sulfate in this important clinical trial that we see is there a difference between products, we will see if (?) is better or not, et cetera.

This is very important because we can make the statement that chondroitin sulfate in Europe, we have a lot of clinical data that proves that the product works, is efficacious and safe in symptomatic treatment. What happened in the United States--and you know better than me. I apologize. You know better than me that there are a lot of nutraceutical products, and this paper that now I am here speaking analyzed the contents of glucosamine and chondroitin sulfate and several U.S. drugs. And this study concluded that the amounts found were significantly different from

label claim in some products with deviations from 0 to 115 percent.

It also evidenced that characteristics such as molecular weight, flexibility of structure, sulfation, and method of manufacture may influence oral absorption. And that is very important because maybe they could have some different clinical effects and maybe could have problems for doctors that recommend those products or the patients. I think this is very important. When we speak about chondroitin sulfate, the more clinical trials published with this chondroitin sulfate, no?

In this case, we see that among all products compared, the one from Bioiberica was the highest permeability rate.

This is very important. In conclusion, in order to ensure equivalent clinical results in terms of efficacy and safety, other chondroitin sulfate products must show their bioequivalence to the reference formulation. It's very important. This is like the same in generics. You must perform an equivalence study. If not, you cannot

say that they are equivalent products. For me it's very clear as a clinical pharmacologist.

For this purpose, we propose the following method to determine the bioequivalence of two chondroitin sulfate formulations, and we propose a method that if some people are interested, they have some copies that we present, for instance, in the 47th annual meeting of the Western Pharmacology Society in Hawaii in January. And now it's near to be, you know, approved and is submitted for publication in the proceedings of the Western Pharmacology Society. And this method we can compare if one product is bioequivalent to the reference product, in this case the reference product that is in clinical trial that is our chondroitin sulfate. I would not like to explain the method, but if there are some person that is interested I can explain this interesting method.

That is all. I apologize for my English, my Catalan English, and thank you very much for your attention.

DR. MILLER: Thank you.

Any comments or questions from the committee?

DR. FELSON: I guess I would like to go back to the chondroitin EULAR recommendation, which I agree with you, I think was an important milestone. The effect sizes listed are derived from a couple of trials that just show enormous effect sizes.

DR. VERGES: Right.

DR. FELSON: One shows an effect size of three times the efficacy of a knee replacement. The effect size there, the range, mostly effect sizes for--you notice how much bigger those effect sizes are than all of the other treatments there? Mostly the effect size of knee replacement--it's actually at the bottom, but it looks like it's not been--it's covered up. It's 1 to 1.7 in the different studies. So chondroitin average effect size looks from those data like it has effect sizes that are equivalent to a knee replacement, which is pretty much as curative as we get in knee OA.

What's going on with that? I've waited

for a number of years to ask somebody from this company why effect sizes--these are not reasonable. They're not--they're on orders of magnitude, logarithmic orders of magnitude higher than effect sizes seen in any other oral preparation in osteoarthritis. They're hard for me to, frankly, believe. Why do you think that your--you know, I don't see patients of mine who have been on these things come back saying, "I don't need a knee replacement," all of them. Okay? What's going on here?

DR. VERGES: Well, this is, you know, the question. We can make the question to experts that they make the recommendations, you know? They made the recommendations in--well, according to the clinical data that is published, and they have this clinical data and they make these recommendations, no? But I cannot answer you because this is the recommendation of the experts according to the literature, and also there are some people in this committee, biostatisticians and clinical pharmacologists, that they put like this. But, you

know, for me as a clinical pharmacologist, the effects of chondroitin sulfate is very clear because I mentioned before it's 50 percent more than placebo. And this is published in a lot of clinical trials that are published in Europe.

DR. FELSON: Be careful, because that effect size is the difference between chondroitin and placebo in those studies.

DR. VERGES: I know. I know. No, no, but in terms of--in my opinion, in terms of the evidence that (?) for me is very clear in terms of clinical--and, in fact, you know, we approved in Spain the chondroitin sulfate two years ago, and the Spanish agency is the number three highest and most respected agency. And, well, it's like this, you know.

I can tell you, as a clinical pharmacologist sometimes when I make a clinical trial I ask the question if my mother would be in the clinical trial or not, no? Another issue is the mother-in-law, no? But my mother--yes, that is another issue, heh? But my mother is taking

chondroitin sulfate and is doing very well. That means that is not the level of evidence is zero. But I can tell you that, well, patients recognize very well the product works, and I think it's, you know, a very interesting product because it's a very safe product. I think if you can have a reduction of pain and (?) safe product, I think it's very important is osteoarthritis. And you know as a rheumatologist the side effects of NSAIDs and analgesics. You know, for example, the paracetamol, you know, the group from Montreal published and said when you use higher doses of paracetamol, you can have also side effects. It is not free of side effects.

We can ask this question maybe in the meeting on Friday. I will ask coming from you this question to the panel about explaining this.

DR. DWYER: Just two further questions about that, perhaps to Dr. Felson rather than to you. First of all, would you please define "effect size"? And, secondly, aren't those two conditions at very different stages along a progression of

disease?

DR. VERGES: The question is for me or the panel?

DR. DWYER: It is for somebody to define "effect size," and then to answer if those two patients who are taking the chondroitin are really the same as people who are getting--who have just had a replacement.

DR. FELSON: I'll be happy to try to address it, I guess. An effect size, the way this was done, is the change in treatment of the active treatment group minus the mean change in the placebo group divided by the standard deviation at baseline of the outcome measure for both groups. Sometimes it's for the placebo group and sometimes it's for both groups, the denominator, and I don't know which was used here.

The answer to your question is surprisingly yes, but it would bias in favor of a higher effect size for a knee replacement because people would be worse and have more room to improve, and, therefore, have higher effect sizes

at the point when they were eligible for their knee replacement. That makes this high effect size, frankly, even more hard to believe.

One of the effect sizes for one of the chondroitin trials in our meta-analysis was 4.5. That's at least three times as good as a knee replacement, if that's possible.

DR. MILLER: Any other comments or questions? If not, thank you very much.

DR. VERGES: Thank you very much.

DR. MILLER: The last speakers are Dr. Todd Henderson and Dr. Chuck Filburn from the Nutramax Laboratories. You have 15 minutes together.

DR. HENDERSON: I want to thank you for the opportunity to present this data. I also wanted to give a clarification that when we looked at presenting information, our understanding was that we were supposed to present information about the petitioners, the petitions. And, evidently, the guidelines that were set down at the beginning were slightly different, but I hope our information

is still very relevant as we are the only other manufacturer of a nutritional product here to present kind of a different perspective than the scientists that have been here thus far.

I will give you a little bit of background. We actually initiated the use of glucosamine and chondroitin sulfate combination in the United States. We're the first company to do that. Certainly our company is dedicated to quality. We're also committed to research. We've published over about 20 research papers on our products, on our brands, Cosequin in veterinary medicine--I am actually a veterinarian and was involved in a lot of those trials--and Cosamin, the human product. As Dr. Verges had pointed out, the chondroitin sulfate that's being used in the NIH study is the same chondroitin sulfate that we have in the United States.

One of the things that we did want to talk about is really how to characterize these compounds, and we feel that really being kind of in throes of this industry, there's a lot of different

quality and there's a lot of different products out there. And I guess one thing that we're concerned about is with any type of claim that may be given, if it's a broad, sweeping type of claim, many different products would take advantage of that, and I'm not sure that would necessarily be fair to the consumer. We certainly support accuracy and truth in labeling.

We would recommend that both health claims be denied, primarily due to the characterization of the materials. The work that's been done has been done on very specific materials, and there's a lot of materials out there that the consumers are going to be trying to pick up from the shelves that are not all going to be the same. And I'm not sure how you handle that question, other than perhaps looking at methods that might be able to try to get to that answer. And I'd like to introduce Dr. Chuck Filburn. Dr. Filburn is our Ph.D. biochemist, head of our research lab, and he was with the National Institute of Aging for 26 years.

DR. FILBURN: Thank you. It was very

interesting hearing your earlier discussion of what is a healthy individual, particularly in aging. Of course, you realize aging is a fatal condition. That is something we talked about a lot.

At issue here, as Todd mentioned, of all the products out there for which a health claim might be granted, what do we really know about them? And our key questions, there are two really fundamental questions here: What is actually in the bottle? And in a sense, that's what was actually used for the research for which the claims were being supported. And does it work? Again, does it work for what's in the bottle that's being offered to the consumer. And that requires both clinical research, a lot of which, as you heard from Dr. Verges, was involved with the same chondroitin sulfate that we use, but also studies on bioavailability which has been done on very few products on the market. But also in terms of characterizing what is in the bottle, there is a need to be sure what the compound is, an identity test, be accurate about how much is there, and

quality or purity, which is the flip side of identity. If there are no other, say, GAGs there, fine. But if there are other ones, then that gets to be an issue.

So let me address these concerns one after the other with regard first to the first petitioner and then the second one.

Just to reiterate what you heard before, the majority of the published clinical studies conducted on chondroitin sulfate were performed with specific, highly purified, 95-percent minimum material from Bioiberica, which we use. This specific chondroitin sulfate has been chosen for the NIH study, and it has been studied in combination with glucosamine hydrochloride for several additional clinical studies on humans, on companion animals, research animals, and was used a lot in basic research. No information has been provided by Petitioner A to support the assumption that these same results were obtained with less purified, less well characterized forms of chondroitin sulfate. The forms available to the

public differ considerably in source, sulfated disaccharides, molecular weight, purity, and often failed to meet label claims. The presumption of a similar clinical response from the various chondroitin sulfate sources currently available to the public is simply unjustified.

The same petitioner, through a letter from its attorney, stated that the evidence is extremely strong of an actual disease-reducing effect: "repair and rebuilding of the cartilage matrix." There is no claim or direct data in the petition, nor that we are aware of, that substantiates this statement.

The petitioner relies solely on what we call the CPC--cetyl pyridinium chloride--method to assay chondroitin sulfate, with no procedure to prove identity. The CPC method detects sulfated GAGs, which could be forms other than chondroitin sulfate. While the petitioners cite methods that use the CPC to detect sulfated GAGs, they do not address the issue of proof of identity, that what is being measured is actually chondroitin sulfate.

The chondroitin sulfate supplement industry as a whole suffers from a lack of uniformity and full validation of acceptable methods. Until this issue is resolved and consumers can actually rely on labeling and claims of joint support from all manufacturers, it is just inappropriate to allow a health clam on a material that in most products lacks careful characterization, especially regarding identity or purity, source, and substantiation of bioequivalence and effectiveness.

With respect to the second petitioner, it has already been drawn to your attention that it's not glucosamine sulfate that's been used for the NIH study but glucosamine hydrochloride, which is considered really the glucosamine base to be the active form of this. And I won't really spend much talking about that. That's already been discussed before.

The contention that the sulfate plays an important role in this, while present in the original petition, seems to have been understated today, and we think that is highly questionable and

will again repeat that it's glucosamine that's talked about most of the time and we think is responsible for most of the effects.

Now, we also get at the issue of assays and accuracy in determining what is in the bottle. The petitioner claims to have a validated assay that in the supplement to the petition stated that it is specific, accurate, and precise, and that is based on a potentiometric measurement. I question the claim of specificity of this assay. I have examined the attachment and found no data showing specificity for glucosamine sulfate. Many organic molecules with a primary amine group will give the same result as glucosamine when titrated as described. The petitioner claims a lack of activity from excipients as evidence of specificity. The petition also criticizes the USP method while at the same time offering it as an indicator of the exact composition of the glucosamine sulfate for which the claim is sought.

It is obvious that there is a clear need for an alternative, specific, commonly used assay

method that must be used in analyzing both petitioner's glucosamine sulfate and others on the market to ascertain what is actually present and being studied clinically.

Again, petitioner is asking for a claim for crystalline glucosamine sulfate. I think that should be clearly defined. This was discussed a little bit earlier. There are actually three ways one could get that: prepare glucosamine sulfate by a method that has a patent on it; dissolve it along with sodium chloride and crystallize it--that's called--I think is their term for crystalline glucosamine sulfate; take sodium sulfate with glucosamine hydrochloride, dissolve them, crystallize them, you can have co-crystals. One could just take the two mixed salts and mix them together. We really don't know what is going on in the industry but suspect the latter is a characteristic of most products, and yet that may dramatically affect stability. That is important in maintaining what is in the bottle because once it is ingested and dissolved in the stomach,

they're all equal. So what is the claim really on?

Again, our own studies have confirmed that recent studies of the contents of glucosamine--whether it is the hydrochloride, whether mixed with chondroitin sulfate, or glucosamine sulfate salts--in many commercial products but particularly glucosamine sulfate showed levels substantially less than that claimed on the labels. This situation reinforces the importance of consistent methodology and accuracy, or truth, in labeling.

I agree with Dr. Arnot that we need to educate the public, but I think this is a key component of that education, and I can't see how you can decide on whether to give a health claim if you don't fully appreciate how important these issues are.

Thank you.

DR. MILLER: Comments or questions?

DR. BLONZ: So, in essence, you are arguing that without good manufacturing practices in place, there should be no consideration, this should be rejected. So it's the GMPs that are the

issue, not the substance?

DR. FILBURN: The GMPs assure the substance, hopefully. The assay methods assure the substance. Even a good GMP with a bad assay method is not going to be any good. The industry and various components of the industry--the USP, the Institute for Nutraceutical Advancement and others--are working towards this end, and we are working with them. But we have been doing this for a long time, and we see a serious problem and we don't think it has been resolved.

DR. MILLER: Dr. Callery?

DR. CALLERY: We just heard, I guess an hour ago, that there was a liquid chromatography, mass spectrometry assay that was validated that would be very specific for glucosamine. If that turned out to be a validated and acceptable assay method, would you change your position?

DR. FILBURN: Well, we think we have a validated assay method that's a little different from one that's in the USP. The one that's been proposed by the Petitioner B, that would be an

excellent method. However, that involves extremely expensive instrumentation and may actually be overkill. I think that was particularly useful in doing bioequivalence studies, and I must commend them on what they did there, what they were able to show, although they used heroically high doses of glucosamine sulfate to achieve those amounts in the blood, you must appreciate. But that's what we're after, yes, used by everybody and commonly acceptable validated assays.

DR. MILLER: Dr. Felson?

DR. FELSON: In your written petition, in the first paragraph you comment on something you didn't mention in your talk: "Recent clinical studies on glucosamine sulfate that lacked industry involvement in analysis and description of data have not found the benefit previously observed in studies supported by Rotta."

Do you want to comment on that?

DR. FILBURN: That was taken word for word from a review paper that I gave heavy weight to, and I didn't want to mix the words, and I took--

this is from the McAlindon review paper which we cited in our comments. And I take it for what it says. I didn't change the wording so that it wouldn't be misinterpreted.

DR. MILLER: Dr. Russell?

[No response.]

DR. MILLER: Dr. Dickinson?

DR. DICKINSON: I just wanted to comment that the GMPs alone I don't think would resolve this issue in the absence of a quality standard, that is, GMPs are process-oriented and don't necessarily in and of themselves define a quality standard. So I think it needs to go beyond just having the GMPs in place, although we will certainly welcome having those in place.

My comment for you is that there are other examples of approved health claims, including the ones for folic acid and for calcium, where there are some criteria specified in the claim for the ingredient--in one case that it meet USP disintegration or dissolution methods, in another that it be limited to certain compounds that FDA

has concluded as GRAS. Would that kind of an approach resolve your issue?

DR. FILBURN: Not yet, because the USP monograph is still in development. We helped produce improvements both in the CPC assay and in the early old-style electrophoresis procedure to prove purity, and that hasn't been fully resolved. And as I understand, there has been emphasis or there may be an obligation--I'm not clear about this--by FDA for the food component to work with AOAC or someone who is developing their own methods. And they're not always the same. There is more than one way to do this, but each one has to be validated and we strongly believe should have a component of identity, and many of them lack that. You can get enough to show up in a CPC assay, but is it really chondroitin sulfate, or what else is there? Are you putting enough junk in to get enough chondroitin sulfate to show up? That actually is what is happening out there. That's why we're here to object to you allowing the health claim.

DR. MILLER: Dr. Kale?

DR. KALE: Not disrespectfully, if it had been your product that was now being considered for the application, would you feel the same way? Or why, perhaps a different question to ask the same kind of thing, didn't you apply for the same privilege of making the claim that's being made by the two parties?

DR. FILBURN: I should probably let Dr. Henderson answer that, but I think--and if I'm incorrect, say so, Todd--had we gotten it, would be it be specific to us? Would everybody be benefiting? Would the consumer be screwed? Pardon the language.

DR. KALE: That's a different product.

[Laughter.]

DR. FILBURN: No, I'm serious about that. Because of this issue of quality, what has happened is a lot of--Nutramax--I came from NIH. Evidence-based research, small company, I was totally impressed with what they had invested in research. And yet the biggest beneficiaries of that are a lot

of other companies that don't adhere to the same standards. So that's all I'm trying to do here.

DR. KALE: I understand. My question was twofold, really. One is: Do you disbelieve the data generated by the other companies, whatever they're serving up in this area?

DR. FILBURN: Some I do, some I don't. But the issue is what assay methods did they use to characterize what they studied and were they adequate for us to really know what they studied.

DR. MILLER: Dr. Harris?

DR. HARRIS: Yes, I'd like to follow up on that question. As I understand it, a source of chondroitin sulfate is shark. Is that correct?

DR. FILBURN: It can be--from our knowledge of what's on the shelves, it can be beef, different parts of beef, trachea usually; pig; or shark. The only ones that we have been involved in clinical testing on are beef trachea, highly purified.

DR. HARRIS: Okay. My concern is apparently you see no reproducibility then if one

uses a standard source of chondroitin sulfate and works from there.

DR. FILBURN: All I can comment on are some preliminary studies that we have done and constantly trying to improve our *in vitro* models to address just that question. And we do find that in some of these tests--I don't want to get into detail, but we don't get the same effects at different doses. It's just not there, and some of them have no effects at all.

DR. HARRIS: One further comment regarding your mention that there could be other factors that could be present. Is it not true that the 4 and the 6 isomer of chondroitin sulfate are the major components? And what would you then consider to be a tolerable acceptance of any other type of--

DR. FILBURN: Well, I think this is a good question. It's an issue that USP has tried to deal with in that they used--we've helped them develop an electrophoretic procedure that we were convinced couldn't be--was not better than detecting 2 percent or more of any other GAG. Beef cartilage

has a lot of keratin sulfate--some keratin sulfate. It will probably behave exactly the same in the CPC assay. You could get other--I'm not clear on--my whole point is that that assay is based on sulfated GAGs, and there's a large range of different sulfated GAGs. So you need something in addition to that, an identity test.

DR. MILLER: Dr. Zeisel?

DR. ZEISEL: Just to clarify for myself, I'm a little confused. I've heard statements that only the Bioiberica product, the Nutramax product, has clinical data of efficacy. And I heard from Rotta that only their product is the product. So could we maybe break down for the human clinical trials that report efficacy, which products are used, all of them, none of them, some of them, so that if we have to decide that one showed efficacy rather than the others, how would we figure that out?

DR. FILBURN: Well, this may help a little. Our studies have all been done on a combination of glucosamine and chondroitin sulfate,

and any that we have done have been on glucosamine alone, not clinical but biochemical, have just been done on glucosamine hydrochloride. And I really can only speak to those studies. You need to distinguish most of--Bioiberica supplies chondroitin sulfate, we use it, combine it with glucosamine hydrochloride. We do not use glucosamine sulfate. We think if they're given in equal amounts, perhaps they will have bioequivalence, but I think one needs to show that because we don't know enough about stability and we know on a label, a milligram basis, there's 63 percent of the total weight as glucosamine and glucosamine sulfate, but 83 percent in glucosamine hydrochloride. So you're not getting the same amount of glucosamine. And if that's the active base, the active form, then you're already starting off on an unequal footing.

DR. MILLER: Thank you very much. I think that leads me into making a couple of comments before we adjourn for the day.

I want to repeat again, the function of

this committee is not to evaluate the petitions that were submitted, but the results of the petitions there is to give you some idea, as many of you already well knew, of the methods that were being used in order to support the petition, and the question is: Are these valid methods? Do they predict what they supposedly claim to be predicting? And so on. So while this is a very interesting discussion, it really is not germane to the issue of the work of the committee, and I think it's very important to make that point.

Secondly, in order to clarify some of these issues, FDA prepared a statement, again, trying to redefine what the role of the committee is, and I'll just read this to clarify: The committee's task is not to evaluate whether there are sufficient data to conclude that glucosamine and/or chondroitin reduce the risk of osteoarthritis; rather, the committee should address the scientific questions that were provided to it. For the committee's information, the evidentiary standard applied to health claims is

different from and weaker than the drug standard. As I indicated this morning, FDA, not the committee, will apply that standard. I think that's important because many of you have experience with drug evaluations, and that's a different standard than used for foods. I think you have to keep that in mind.

We finished a half-hour earlier, and rather than try to start something new, I suggest we adjourn for the day, and I suggest you take another glance at the questions, which are under Tab 5 in your book.

We meet again tomorrow morning at 8 o'clock.

[Whereupon, at 4:30 p.m., the meeting was adjourned.]

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